PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HKQ-PB60286	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2004/005966	International filing date *(day/month/year)* 01.06.2004	Priority date *(day/month/year)* 03.06.2003
International Patent Classification (IPC) or both national classification and IPC C07C59/48, C07C59/52, C07C59/56, C07C59/58, C07C59/68, C07C59/86, C07C233/33, C07C255/57, C07C291/14, C07C321/26, C07C323/33		
Applicant GLAXO GROUP LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.01.2005	08.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Romano-Götsch, R Telephone No. +49 89 2399-8874

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP2004/005966

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-27 as originally filed

Claims, Numbers

1-5 received on 28.01.2005 with letter of 25.01.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1 (part), 3-7 (part)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1 (part), 3-7 (part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-5
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1,2,4,5 (3: no opinion)
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III.

Claim 3, which is directed to a method for treatment of the human or animal body by therapy, contains subject-matter which no International Authority shall be required to examine (Rule 67.1(iv) PCT). Consequently, an opinion in respect to the industrial applicability of said claim is not established in the present opinion.

Re Item V.

The following document is referred to in this communication:
D1: Barron et al., *Jnl Med. Chem.*, 11(6),1968, 1139-1144, XP002147476

Novelty

New claim 1 is directed to 3-hydroxypentanoic acids substituted by a biphenyl in position-4, said biphenyl optionally forming a tricyclic ring system.
D1 reports the activity as anti-inflammatory of 4-biphenylyl-**3-hydroxybutyric** acid, 4-biphenylyloxy-3-hydroxybutyric acid (Table I) and their derivatives (Table II).
In view of the structural differences with the compound of claim 1 on file, said claim is deemed to be novel (Art.33(2) PCT).
Dependent claims 2-5 meet as well the requirements of the PCT in respect of novelty (Article 33(2) PCT).

Inventive Step

Departing from D1, the problem to be solved by the present application, is the provision of novel matrix metalloprotease inhibitors.
The solution proposed in present claim 1 is the provision of **3-hydroxypentanoic** acid substituted by a biphenyl in position-4, said biphenyl optionally forming a tricyclic ring system. In other word, the solution proposed in the application consists in the alteration of the side chain of the 4-biphenylyl-**3-hydroxybutyric** acid by prolonging the side chain of one carbon atom.

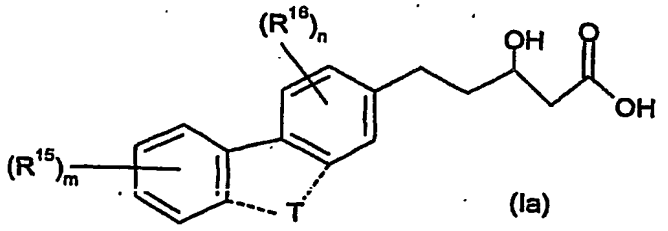
D1 teaches that, departing from 4-biphenylyloxy-3-hydroxybutyric acid, the 4-biphenylyl-3-hydroxybutyric acid is the compound with highest antiinflammatory potency (compare the activities of compound 31 in Table I vs. compound 67 of Table II; compound 33 in Table I vs. compunds 70, 73).
D1 teaches also that alteration of the side chain had a marked effect on antiinflammatory activity (p.1141, right column) and aryloxy derivatives analogues were much less active.
In view of D1, there is no incentive to modify the side chain of 4-biphenylyl-3-hydroxybutyric acid. Thus, claims 1-5 are thus considered inventive (Art.33(3) PCT).

Industrial applicability

For the assessment of the presently worded claim 3 on the question whether they are

industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not regard as industrially applicable claims to the use of a compound in medical treatment, however will allow claims to a known compound for first use in medical treatment and the use of such compound for the manufacture of a medicament for a new medical treatment.

1. A compound of formula (Ia):



(Ia)

wherein:

T is absent or represents O, S, NR^{17} or $CR^{17}R^{18}$;

--- represents optional bonds;

R^{15} and R^{16} each independently represents halo, cyano, nitro, OR^{17}, SR^{17}, COR^{17}, $NR^{18}COR^{17}$, $CONR^{17}R^{18}$, optionally substituted phenoxy or C_{1-6} alkyl optionally substituted by OR^{17};

R^{17} represents H, C_{1-6} alkyl or C_{1-4} alkylaryl;

R^{18} represents H or C_{1-6} alkyl;

m and n each independently represents 0 or an integer 1,2 or 3;

with the proviso that when T is absent, R^{15} does not represent $NR^{18}COR^{17}$or $CONR^{17}R^{18}$ in the ortho position; and physiologically functional derivatives thereof.

2. A compound as claimed in claim 1 for use in medicine.

3. A method for the treatment of a human or animal subject suffering from or susceptible to an autoimmune disorder or an inflammatory condition which method comprises administering to said human or animal subject an effective amount of a compound as claimed in claim 1.

4. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment of inflammatory conditions or autoimmune disorders.

5. A pharmaceutical composition comprising a compound as claimed in claim 1 and a pharmaceutically acceptable carrier therefor, and optionally one or more other therapeutic agents.